REMARKS

Claims 3, 4, 6, 9, 11, 18, 20, and 21 have been canceled, without disclaimer of the subject matter recited therein. Claim 1 has been amended to incorporate the limitation of canceled claim 3. Accordingly, no new matter has been entered by these claim amendments.

Rejection Under 35 USC § 112, 1st Paragraph - Enablement

Claims 1, 3-9, 11, 13, 14, 16-18, 20, 24, and 25 are rejected under 35 USC §112, first paragraph, for alleged lack of enablement. Specifically, *inter alia*, the Examiner asserts that the claims broadly encompass any polymorphism at codon 594 of ESR1, and concludes that the claimed subject matter is not described in the specification in such a way as to enable one skilled in the art to make and/or use the claimed invention. Claims 3, 4, 6, 9, 11, 18, 20, and 21 have been canceled, rendering this rejection moot as applied to these claims. This rejection is respectfully traversed as applied to the remaining claims.

Specific Polymorphism. Applicants have amended claim 1 to specifically recite detection of a polymorphism at a fragment of exon 8 of an estrogen receptor (ESR1) gene that encodes codon 594 of an estrogen receptor protein, where the polymorphism consists of "a guanine to adenine change at nucleotide 2014 of the ESR1 gene." Accordingly, the amended claims encompass detection of a specific polymorphism. This polymorphism and its association with migraine is set forth in the specification (see, e.g., page 7, lines 3-9 and page 20, lines 10-26).

Dependent claims further recite a polymorphism in intron 7 of a progesterone receptor gene that includes a 306 bp insertion. This polymorphism and its association with migraine is set forth in the specification (see, e.g., page 7, lines 3-9 and page 21, line 25 to page 22, line 7).

Methods of detecting the G2014A polymorphism in a nucleotide sequence according to the amended claims are amply described in the specification, for example, at pages 11-14, and include nucleic acid sequence amplification (e.g., as described at page 11, line 26 to page 12, line 10) in conjunction with restriction fragment length polymorphism analysis (see, page 12, lines 14-19) and/or direct sequencing (see, page 13, lines 21-25); bidirectional PCR amplification of specific alleles (see, page 12, lines 28-30); allele-specification oligonucleotide hybridization (see, pages 13, lines 1-3); fluorescence-based melt curve analysis (see, page 13, lines 4-15); denaturing gel electrophoresis (see, page 13, lines 16-20); mass spectroscopy (see, page 13, lines 26-29); and

microarray analysis (see, page 13, line 30 to page 14, line 15). Accordingly, clear guidance for the detection of a polymorphism is provided.

Additionally, the present description provides working examples of determining whether an individual has a predisposition to migraine, including analysing a biological sample from the individual for a polymorphism in the estrogen receptor gene and the progesterone receptor gene (see, page 17, line 20 to page 24, line 2). As discussed at page 20, lines 21-23, individuals who carry the 594A allele in the ESR1 gene are 1.8 times more likely to suffer from migraine than those who do not carry this allele, and the interaction of the PGR PROGINS insert combined with the 594A allele in the ESR1 gene increased migraine risk by 3.2 (see, page 25, lines 13-16).

Provided herewith is a Declaration under 37 CFR 1.132 by inventor Lynette Robyn Griffiths. As discussed below, the Declaration addresses the assertions made in the Office Action regarding the predictability of the art and, as a result, the enablement of the claimed subject matter.

Association of G2014A polymorphism with migraine in Applicants' replication study. The Office Action focuses on specific subpopulations in Applicants' replication study and asserts that the two studies are conflicting. Specifically, the Office Action asserts that Applicants' own replication study failed to provide statistically significant correlations for ESR1 polymorphism in codon 594 and migraine for certain subgroups in the replication study. The Office Action appears to focus on the fact that a statistically significant correlation did not occur in the replication study for males, nor in the migraine without aura (MO) subgroup. As pointed out in paragraph 3 of the Declaration, this lack of association in these subgroups does not indicate that a statistically significant correlation does not exist between the two independent case-control populations. Rather, the lack of association reflects the small number of males and MO sufferers in the replication study. This point is also addressed in the specification (see, page 20, lines 29-32). Thus, the Office Action ignores the fact that when viewing the two independent case-control populations overall, the ESR1 G2014A (rs2228480) polymorphism was found to be positively associated with migraine, as seen in genotype frequencies of $P=0.008$ and $P=4x10^{-5}$, respectively.

The Declaration (see, paragraph 4) also points out that for the PGR PROGINS polymorphism, the same two independent case-control populations also showed association with

migraine in the total group analysis: population 1 genotypic P=0.04, population 2 genotypic P=0.019.

Thus, although the Office Action focuses on specific subpopulations in Applicants' replication study, the Declaration makes clear that a positive association of the G2014A polymorphism with migraine is borne out by the two independent case-control populations overall.

Follow-up studies. The Office Action also focuses on particular follow-up studies and asserts that several of the studies teach that no association was found for the G2014A (rs2228480) polymorphism and migraine. As further discussed in paragraphs 5 and 6 of the Declaration, the results of a systematic review and meta-analysis on the association between ESR1 gene polymorphisms and migraine provide independent confirmation of the conclusion found in the instant specification, namely, that the ESR1 G2014A (rs2228480) polymorphism is associated with migraine (see, Exhibit B of Declaration, hereinafter "Schürks et al."). Specifically, the meta-analysis of Schürks et al. concludes that the A allele is associated with an increased risk for any migraine (see, Schürks et al. at page 1312).

Thus, in view of the accompanying Declaration, it is submitted that results from the two independent case-control populations presented in the specification, when considered in total, and the study of Schürks et al. support an argument that pending claims 1, 5, 7, 8, 13, 14, 16, 17, 24, and 25 are indeed enabled by the specification as filed, and that undue experimentation would not be required of the skilled artisan to make or use the invention as claimed.

In view of the above arguments, reconsideration and withdrawal of the rejection under 35 USC § 112, first paragraph is respectfully requested.

No Disclaimers or Disavowals

Although the present communication may include alterations to the application or claims, or characterizations of claim scope or referenced art, Applicants are not conceding in this application that previously pending claims are not patentable over the cited references. Rather, any alterations or characterizations are being made to facilitate expeditious prosecution of this application. Applicants reserve the right to pursue at a later date any previously pending or other broader or narrower claims that capture any subject matter supported by the present disclosure, including subject matter found to be specifically disclaimed herein or by any prior prosecution.

Accordingly, reviewers of this or any parent, child or related prosecution history shall not reasonably infer that Applicants have made any disclaimers or disavowals of any subject matter supported by the present application.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

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By: _____

Brent C. Moore
Registration No. 55,461
Attorney of Record
Customer No. 20995
(858) 707-4000

11369114
060611